Contains Nonbinding Recommendations

Draft Guidance on Risperidone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Risperidone

Dosage Form; Route: Injectable; intramuscular

Recommended Studies: Two studies: In vitro and in vivo

1. Type of study: In vitro drug release
   Strength: 25 mg/vial

Medium:	Dissolution medium (pH 7.4), prepared as indicated below
Volume:	400 mL (200 mL for each temperature)
Apparatus:	Cylinder bottle
Temperature:	37°C and 45°C (water bath)
Sampling times:	Day 1 and Day 21 for 37°C Multiple time points from Days 0 to 8 for 45°C. Two sampling time points, that bracket $T_{50\%}$ (which is defined as the time of 50% drug release), are to be linearly interpolated to determine $T_{50\%}$.

Parameters to measure: Cumulative drug release at Days 1 and 21 at 37°C, cumulative drug release at Day 8 at 45°C, and $T_{50\%}$ at 45°C

Bioequivalence based on (90% CI): $T_{50\%}$. The 90% confidence interval (CI) of the test/reference ratio of $T_{50\%}$ should be within 80-125%.

These data are to be submitted in addition to the method specified in the Dissolution Methods Database (see below), which is to be used for stability and quality control testing.

Preparation of dissolution medium (makes 20 L):

- Add 40 g sodium azide into 760 g deionized water
- Add 18.76 kg deionized water into a 20 L container
- Add 200 g 1M HEPES buffer solution into the container
- Add 116 g sodium chloride to 1 kg deionized water
- Add sodium chloride solution into the container
- Add 80 mL sodium azide solution into the container
- Add 4 mL Tween 20 into the container

- Aliquot the prepared solution into four separate 5 L containers. Measure the pH of each aliquot and adjust it to 7.4 ± 0.1 with dilute sodium hydroxide or HCl as needed. After pH adjustment, measure the osmolality of each aliquot. If the osmolality of the aliquot in each container is not within the range 200 ± 20 mOsm, discard the entire batch of media and prepare a new batch.

As per 21 CFR § 314.94, the proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product for all strengths (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial).

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2. Type of study: In vivo, steady-state, fasting
Design: Crossover strength: 25 mg/vial
Subjects: Patients who are already receiving a stable regimen of risperidone long-acting injection via the intramuscular route. Patients who are already receiving 25 mg of risperidone long-acting injection every two weeks would be eligible to participate in the study by continuing their established maintenance dose.
Additional comments: FDA recommends that studies not be conducted using healthy subjects or patients on a different antipsychotic treatment.

Analytes to measure (in appropriate biological fluid): Risperidone in plasma

Bioequivalence based on (90% CI): Risperidone

In the evaluation of bioequivalence of the multiple dose study, the following pharmacokinetic data should be submitted for risperidone:

- Individual and mean blood drug concentration levels in a dosing interval after steady state is reached
- Individual and mean trough levels (C_{min} ss)
- Individual and mean peak levels (C_{max} ss)
- Calculation of individual and mean steady-state $AUC_{interdose}$ ($AUC_{interdose}$ is AUC during a dosing interval at steady state)
- Individual and mean percent fluctuation [$=100 * (C_{max}$ ss $- C_{min}$ ss$)/C_{average}$ ss]
- Individual and mean time to peak concentration

The log-transformed AUC and C_{max} data should be analyzed statistically using analysis of variance. The 90% CI for the ratio of the geometric means of the pharmacokinetic parameters (AUC and Cmax) should be within 80-125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product. The

trough concentration data should also be analyzed statistically to verify that steady state was achieved prior to pharmacokinetic sampling.

In period 2 (when patients are switched from reference to test or vice versa), individual and mean blood drug concentration levels should also be reported during the third dosing interval (days 28-42). Intensive sampling should be performed during this interval to accurately capture changes in trough and peak levels. This information will be used as supporting data for BE to confirm that any difference in Tlag does not result in significant transient differences in Cmin.

Waiver request of in vivo testing: 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial based on (i) acceptable in vitro and in vivo BE studies on the 25 mg/vial strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro drug release testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).